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Epidemiology

Cadmium, lead and mercury in Norwegian obese patients before and 12 months after bariatric surgery

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ABSTRACT

Purpose: Previous studies have suggested a role for the toxic elements lead (Pb), mercury (Hg) and cadmium (Cd) in the development of insulin resistance and hypertension. Increased blood Pb levels have been reported after bariatric surgery and weight loss. As about 80% of patients undergoing bariatric surgery are women, most of them of childbearing age, there are concerns regarding fetal exposure to toxic trace elements. We measured whole blood Hg, Pb and Cd concentrations in morbidly obese patients before and 12 months after Roux-en-Y gastric bypass (RYGB).

Patients and methods: Forty-six patients eligible for bariatric surgery were recruited at Innlandet Hospital Trust, Norway (2012–2014). The majority were women and 54% were of reproductive age. Whole blood samples were collected prior to and 12 months after surgery. Trace element concentrations were measured using mass spectrometry (HR-ICP-MS).

Results: Median whole blood Pb concentrations increased by 73% during the 12 months study period while Hg and Cd decreased by 31% and 27%, respectively. We found a negative correlation between Pb levels before surgery and BMI ($p = 0.02$). Before surgery patients with hypertension had significantly higher median whole blood Hg levels compared to patients with normal blood pressure ($p < 0.001$).

Conclusion: One year after bariatric surgery, the median whole blood Pb concentration was increased, while Hg and Cd concentrations were decreased. The majority of bariatric surgery patients are women of reproductive age and weight loss is associated with improved fertility. As even low dose Pb exposure during fetal life is associated with negative effects on the central nervous system, the observed increase in whole blood Pb after weight loss causes concern. Further studies are needed to elucidate these observations.

1. Introduction

Globally there is an increasing prevalence of obesity defined by a BMI ≥ 30 kg/m^2, which is known to predispose to comorbidities like type 2 diabetes, hypertension, dyslipidemia and coronary heart disease [1]. Epidemiologic studies have suggested a role for the toxic metals lead (Pb), mercury (Hg) and cadmium (Cd) in the development of metabolic syndrome [2]. All three elements have been shown to interact with obesity in various ways, like substituting for essential trace elements or increasing the risk for developing diabetes [3] and hypertension [2,4,5].

As weight loss is associated with improvement in metabolic function [6], an increasing number of patients are referred to bariatric surgery [7]. Increased blood Pb levels have been reported after bariatric surgery in women [8], and there are concerns regarding the redistribution of mercury (methylmercury) into blood after postoperative loss of fat tissue [9].

About 80% of the patients undergoing bariatric surgery are women, many in their childbearing age [10]. Weight loss is associated with improved fertility rates [11], however, bariatric surgery is also regarded as a risk factor for adverse pregnancy outcomes [12], particularly due to disturbances in micronutrient status [13]. Exposure to toxic

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elements during fetal life and infancy may have serious long-term health consequences for the child, and cause damage to the central nervous system, the lungs and the kidneys [14–17].

We have studied changes in whole blood Hg, Pb and Cd concentrations before and 12 months after Roux-en-Y gastric bypass (RYGB) in a group of patients with a BMI ≥ 35, where the majority were women of reproductive age.

2. Materials and methods

2.1. Study population

Patients aged 18–60 years eligible for bariatric surgery due to a BMI ≥ 40 kg/m^2 or a BMI ≥ 35 with serious weight related comorbidities like type 2 diabetes or cardiovascular disease, were consecutively recruited at Innlandet Hospital Trust, Gjøvik, Norway, during 2012–2014. Exclusion criteria were major psychiatric disorders, serious somatic disorders not related to obesity, alcohol or drug addiction, former obesity surgery and other major abdominal surgery. The enrolled patients got an initial brief dietetic counselling six months before surgery. At the end of this period, they attended an eight week course on lifestyle changes, followed by bariatric surgery. The surgical technique used was laparoscopic Roux-en-Y gastric bypass (RYGB), which involves transection of the upper part of the stomach leaving about 30 mL, which is anastomosed with the distal jejunum, resulting in bypass of the remaining major part of the stomach, duodenum and proximal jejunum [18]. Reduced size of the functional stomach results in earlier satiety and thus restricted food intake. Furthermore, the food in this stomach pouch bypasses the duodenum and enters directly into the distal jejunum, leading to reduced absorption in the small intestine [18].

After surgery the patients were recommended daily supplementation with iron (100 mg), calcium (1000 mg) and vitamin D (20 μg) for 6 months, intramuscular vitamin B12 injections (1 mg) every third month, and lifelong daily multivitamin/mineral supplements.

Ethical approval of the protocol was obtained by the Regional Committee for Medical and Health Research Ethics (REK), Region South-East, Norway, ref. number 2012/1394. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients before enrolment.

2.2. Sample collection, preparation and analysis

Whole blood samples were collected immediately before surgery and 12 months after surgery. The samples were obtained from the cubital vein between 8:00 and 10:30 a.m. and collected in Vacuette Trace Elements Sodium Heparin tubes (Greiner Bio-One) for trace element analyses. The samples were stored at −20 °C before analysis.

Approximately 0.7 mL blood was transferred to metal-free 18 mL teflon tubes. The exact weight of each sample was measured and converted back to volume by multiplying with 1.06 g/mL (the average density of whole blood). The samples were acidified with 1.0 mL 65% (V/V) ultrapure nitric acid, produced in-house from p.a. quality nitric acid (Merck, Darmstadt) using a sub-boiling distillation system (SubPur, Milestone, Shelton, CT). The samples were then digested using a high performance microwave reactor (UltraClave, Milestone). Digested samples were decanted into pre-cleaned 15 mL polypropylene vials (VWR, USA) and diluted with ultrapure water (Purelab Option-Q, Elga) to achieve a final acid concentration of 0.6 M.

Trace element concentrations were measured using high resolution inductively coupled plasma mass spectrometry (HR-ICP-MS, Thermo Finnigan Element 2, Bremen). The sample introduction system consisted of an SC2-DX auto-sampler with ULPA filter, a prepFAST system, a concentric PFA-ST nebulizer coupled to a quartz cyclonic micro mist Scott spray chamber with auxiliary gas port, aluminium skimmer and sample cones, and an O-ring-free quartz torch and 2.5 mm injector (Elemental Scientific, Omaha, NE). The radio frequency power was set to 1350 W; nebulizer and T-connection sample gas flow were 0.75 L/min, and 0.55 L/min, respectively. Cooling gas flow was 15.5 L/min, auxiliary gas flow was 1.1 mL/min and additional gas consisted of 10% methane in argon with flow rate of 0.01 L/min.

Two multi-element stock solutions (Elemental Scientific, Omaha, NE) were used, one serving as a calibrating solution and the other as a quality control. These solutions were matrix matched with the blood samples for acid strength (0.6 M ultrapure nitric acid), and by adding 160 mg/L sodium and 115 mg/L potassium (Spectrapure Standards, Oslo). Corrections for instrumental drift were done by repeated measurements of one of the multielement standards. The stability of the instrument was checked by inspection of the argon signal and measurements of 1 μg/L rhenium added as an internal standard through the prepFAST system. Repeated analysis of a certified reference material (Seronorm Level 1, Sero, Norway) was used to verify the accuracy of the instrument.

2.3. Statistical analysis

Results are presented as mean and standard deviation (SD), compared by Student's *t*-test or Anova, and median and interquartile range (IQR), compared by Mann-Whitney U test or Kruskal-Wallis test. Chi-square test was used for categorical data. Spearman correlations were used to explore relationships between data. Tests of normality were Kolmogorov-Smirnov and Shapiro-Wilk.

Graphical illustration of the relationship between age and whole blood Pb and Hg, alcohol intake and Pb, and smoking history and Cd was obtained by generalized additive models (GAM).

The SPSS statistical program (version 23) and the packages "mgcv" in R®, version 3.3 (The R Foundation for Statistical Computing) were used for the statistical analyses. Two-sided p-values < 0.05 were considered statistically significant.

3. Results

The study population included 46 patients (age range 27–59 years) with baseline characteristics given in Table 1. The majority were women, of whom 21/39 (54%) were of reproductive age (< 45 years).

At inclusion, both women and men tended to eat more meat than fish and seafood (Table 1). Nine of 39 women (23%) and one of six men (17%) were daily smokers (p = 0.08) (Table 1), and the percentage declined from inclusion to 12 months after surgery (22% versus 3%). The number of patients who reported use of alcohol more than once a month, remained essentially unchanged from inclusion to 12 months after bariatric surgery (43% versus 41%).

Total mean weight loss from inclusion to 12 months after bariatric surgery was 42.5 (SD 11.9) kg, (range 13.4–68.7 kg). Approximately 25% of the weight loss was achieved by dieting and exercise before surgery (mean 10.3 (SD 4.6) kg), and 75% was achieved after surgery

Table 1
Baseline characteristics in patients admitted for gastric bypass (n = 46).

Female gender[a]	39/46 (85)
Age, years[b]	43.9 (9.1)
Body mass index[b]	42.4 (3.6)
Education, years[b]	13 (3)
Full time occupation[a]	23/45 (51)
Married/cohabitant[a]	38/44 (86)
Daily intake of meat, grams[b]	164 (60)
Daily intake of fish/seafood, grams[b]	80 (49)
Daily smoker[a]	10/45 (22)
Alcohol intake ≥ 1 per month[a]	20/46 (43)
Current diagnosis of hypertension[a]	15/44 (34)
Current diagnosis of diabetes[a]	7/44 (16)

[a] Data are expressed as number (%).
[b] Data are expressed as mean (SD).

Table 2
Whole blood lead, mercury and cadmium concentrations before and 12 months after bariatric surgery (n = 46).

Parameters[a]	Before surgery N = 46	12 months after surgery N = 46	P value[b]
Whole blood lead, µg/L	6.73 (4.13, 9.48) 1.58 – 17.78	11.66 (7.96, 14.91) 4.73 – 22.94	< 0.001
Whole blood mercury, µg/L	1.08 (0.72, 1.46) 0.38 – 3.97	0.74 (0.57, 1.31) 0.26 – 3.60	0.001
Whole blood cadmium, µg/L	0.33 (0.21, 0.56) 0.12 – 1.96	0.24 (0.16, 0.58) 0.08 – 1.07	0.003

[a] Data are expressed as median (IQR) and Range.
[b] Compared by Wilcoxon Signed Rank Test.

(mean 32.3 (SD 10.6) kg). There was a mean reduction of 33% in BMI from inclusion to 12 months postoperatively (mean BMI 27.8 (SD 3.4), with no gender difference (p = 0.81).

4. Toxic element concentrations before and 12 months after bariatric surgery

Whole blood Pb, Hg and Cd concentrations changed significantly during the observation period of 12 months (Table 2, Table 4). Median Pb concentration increased by 73%, while median Hg and Cd concentrations decreased (by 31% and 27%, respectively).

BMI was significantly inversely correlated to whole blood Pb before surgery (rho = -0.34, p = 0.02), while only weak, negative correlations were observed for BMI and Hg and Cd (p > 0.12). Age was significantly correlated to whole blood concentrations of Pb (rho = 0.39, p = 0.007) and Hg (rho = 0.53, p < 0.001) before surgery (Fig. 1), but not to Cd concentrations (rho = -0.04, p = 0.8).

Reported alcohol intake at inclusion was positively related to whole blood Pb before surgery (rho = 0.44, p = 0.003), with a dose-response relationship between intake of alcohol in units and whole blood Pb, as shown by GAM corrected for age (Fig. 2). Alcohol intake was also the strongest predictor for Pb in a multiple linear regression model, which additionally included gender, age, smoking history, fish intake, education, BMI at inclusion and weight reduction before surgery (Table 3).

Women had slightly higher median Hg levels 1.12 (IQR 0.73, 1.50) µg/L than men median Hg 0.94 (IQR 0.66, 1.01) µg/L before surgery, but this difference was not significant (p = 0.14). However, in the multiple linear regression model, gender was a strong predictor for whole blood Hg followed by intake of fish and seafood (Table 3).

Before surgery, patients with hypertension (n = 15) had significantly higher median whole blood Hg 1.76 (IQR 1.13, 2.01) µg/L compared to patients with normal blood pressure median Hg 1.00 (IQR 0.65, 1.17) µg/L, p < 0.001. This difference was reduced after surgery and was no longer significant (p = 0.19). No differences were observed for Pb and Cd concentrations in patients with a diagnosis of hypertension vs. those without this diagnosis.

Smoking history at inclusion was strongly correlated to whole blood Cd before surgery (rho = 0.69, p < 0.001) (Fig. 3), and was the strongest predictor for Cd in the multiple linear regression model (Table 3).

At inclusion seven patients had a diagnosis of diabetes; no differences in Pb, Hg or Cd concentrations before or after surgery were seen in diabetic versus non-diabetic patients (p > 0.12).

5. Discussion

Studies have proposed a connection between toxic elements, diabetes and obesity [19,20].When these elements substitute for essential micronutrients like iron, zinc or potassium, they may catalyze oxidative stress reactions and damage cells, enzymes and genes [21]. Pancreatic beta-cells may be prone to toxic element-induced oxidative stress due to their high expression of metal transporters and low expression of antioxidants [22].

Metal neurotoxicity on brain function and signaling related to appetite and satiety may also be involved in development of obesity. Since

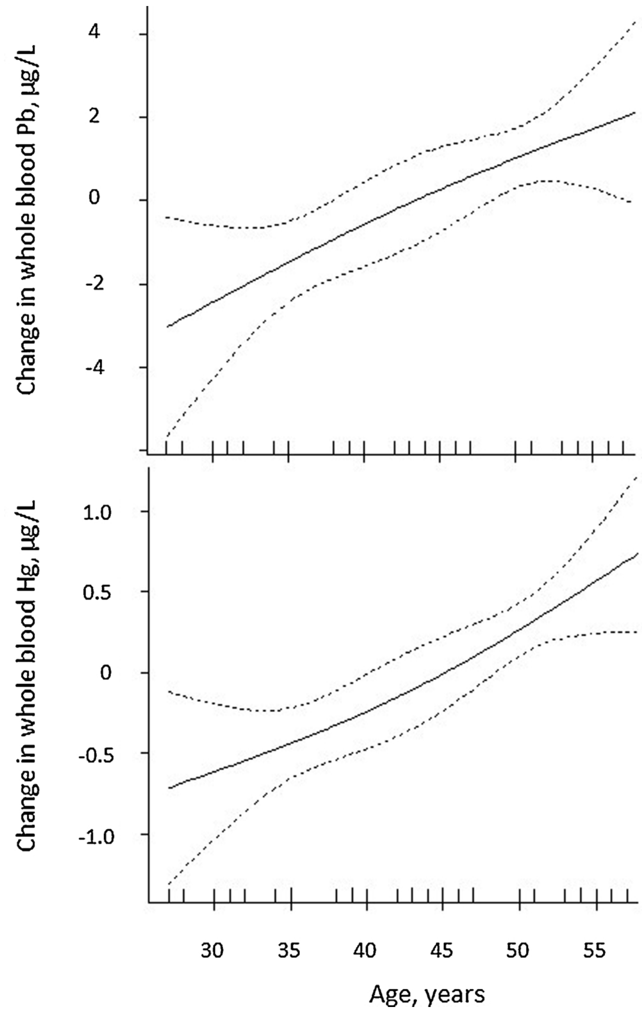

Fig. 1. The association of age with whole blood lead (Pb) and mercury (Hg) concentrations by a generalized additive model (GAM).
The solid line shows the fitted model and the area between the dotted lines indicate 95% confidence interval.

brain development is affected by both lead and cadmium a disruption in energy balance could result from dysregulated appetite and satiety response, with consequent increased caloric intake [23].

Toxic metals such as Cd, Hg and Pb also cause damage by functioning as endocrine disruptors that alter physiological functions. Both Cd and Hg stimulate progesterone synthesis [24].

In the present study, we found the whole blood Pb concentration to be negatively related to BMI in a population of obese Norwegian adults. The median whole blood Hg concentration was substantially higher in patients with hypertension, while no associations were found for any of these metals as related to a diagnosis of diabetes.

One year after bariatric surgery with a mean weight loss of 32.3 kg, median whole blood Pb increased by 73%, while median Hg and Cd concentrations declined by 31 and 27%, respectively. The majority of

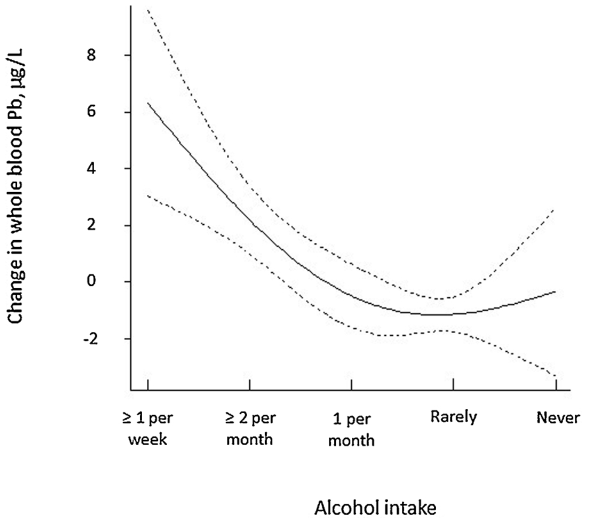

Fig. 2. The association of alcohol intake with whole blood lead (Pb) concentrations by generalized additive model (GAM), adjusted for age.
The solid line shows the fitted model and the area between the dotted lines indicate 95%.

Table 3
Determinants of whole blood lead, mercury and cadmium before bariatric surgery (n = 46) by multiple linear regression[a].

Variables included in the model	Whole blood lead		Whole blood mercury		Whole blood cadmium	
	Beta	P	*Beta*	P	*Beta*	P
Gender[b]	−0.06	0.77	−0.43	0.03	0.04	0.80
Age, years	0.17	0.36	0.27	0.14	−0.05	0.74
Alcohol intake[c]	0.47	0.006	0.23	0.16	0.01	0.95
Smoking history[d]	0.04	0.80	−0.30	0.09	0.49	0.02
Intake of fish and seafood, grams/week	0.03	0.88	0.31	0.08	0.01	0.96
Education, years	0.31	0.05	−0.20	0.21	0.06	0.71
BMI at inclusion	−0.22	0.23	−0.15	0.41	−0.28	0.18
Weight reduction, after dieting, kg	0.21	0.25	0.09	0.62	0.05	0.80

[a] Multiple linear regression; the model contains gender and the initial weight reduction after dieting, in addition to the parameters listed in the table.
[b] Gender: Female, male.
[c] Alcohol intake: Never, rarely, 1/month, ≥2/month and ≥1/week.
[d] Smoking: Never smoker, former smoker and current smoker.

the patients were women of reproductive age (< 45 years). As weight loss is associated with increased fertility, the increase in whole blood Pb concentration may be of concern for pregnancy outcome.

In our population of young and middle aged obese patients, age was significantly positively correlated to whole blood Pb and Hg, while BMI was negatively correlated to whole blood Pb before surgery. Weak negative, however not significant, correlations between BMI and Hg and Cd were observed. Published studies on the correlation between BMI and toxic metals have shown ambiguous results [3,25–27]. However, in large population studies including the US NHANES, an inverse correlation between BMI and whole blood Hg [25], whole blood and urine Pb [3,26] and Cd [3,27] have been reported. Pb and Cd accumulate progressively in the body with a long biological half-life of 15–30 years [28,29], while Hg has a relatively short half-life of approximately 50 days [30]. While both BMI and the levels of Hg, Pb and Cd tend to increase with age, these inverse relations have been difficult to explain, but seem to be independent of age and gender [3].

Table 4
Concentrations of whole blood lead, mercury and cadmium in different populations.

Parameters[a]	Obese Norwegian adults in 2012-14[a]				Norwegian women, 18-40 years in 2011-15 (n = 158)[b]	Finnish women, 31 years in 1997 (n = 123)[c]	Danish women, 18-40 years in 2011-12 (n = 73)[d]	French adults, 20-59 years in 2008-10 (n = 1992)[e]
	All adults, 27-59 years (n = 46)		Women, in reproductive age 27-45 years (n = 21)					
	Before surgery	After surgery	Before surgery	After surgery				
Whole blood lead, μg/L	6.73 (2.58, 12.83)	11.66 (6.31, 18.46)	6.17 (2.10, 10.65)	9.53 (5.24, 15.19)	8.29 (4.14, 22.79)	9.06 (0.80, 91.9)	8.1 (5.3, 15.8)	18.3 (8.86, 38.7)
Whole blood mercury, μg/L	1.08 (0.50, 2.06)	0.74 (0.39, 1.87)	1.00 (0.41, 1.49)	0.64 (0.33, 1.44)	0.99 (0, 3.88)	1.85 (0.33, 11.00)	1.59 (0.69, 5.2)	1.64 (0.47, 3.91)
Whole blood cadmium, μg/L	0.33 (0.18, 1.11)	0.24 (0.11, 0.83)	0.33 (0.18, 1.37)	0.21 (0.16, 1.02)	0.15 (0.08 – 0.87)	0.12 (0.05 – 3.37)	0.2 (0.07, 0.76)	0.37 (0.17 – 1.22)
References	The present study				33	32	34	31

[a] Data are expressed as median (10, 90 percentile).
[b] Data are expressed as median (2.5, 97.5 percentile).
[c] Data are expressed as geometrical mean (min, max).
[d] Data are expressed as geometrical mean (10, 95 percentile).
[e] Data are expressed as geometrical mean (10, 95 percentile).

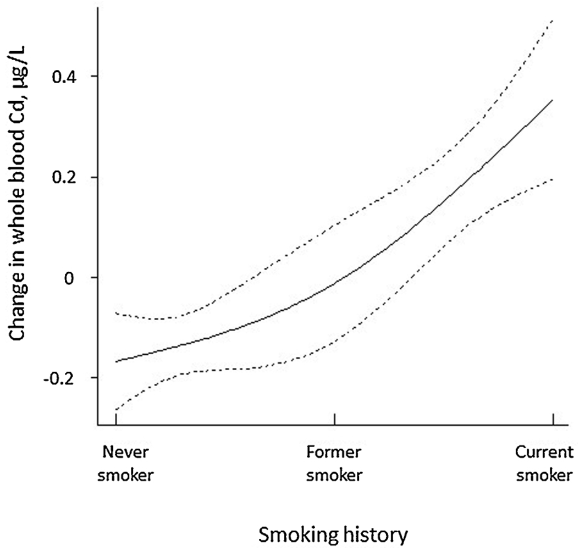

Fig. 3. The association of smoking history with whole blood lead (Pb) concentrations by generalized additive model (GAM), adjusted for age.
The solid line shows the fitted model and the area between the dotted lines indicate 95%.

5.1. Lead

Compared to French adults [31], median whole blood Pb was lower in obese Norwegian adults both before and after surgery (Table 4). However, after bariatric surgery, obese Norwegian women of reproductive age had higher median whole blood Pb concentrations compared to age-matched Scandinavian women [32–34] (Table 4).

A substantial increase of more than 70% in median whole blood Pb concentration was observed after bariatric surgery, in parallel to the weight loss of about 30 kg. The strongest predictor for whole blood Pb at inclusion was use of alcohol, which is in accord with reports by others [33]. Alcohol habits remained essentially unchanged from inclusion to 12 months after bariatric surgery.

More than 90% of Pb is stored in bone [28]. Weight loss has been shown to increase bone turnover, thereby mobilizing Pb with resulting higher blood levels [8,35]. For example, in a small group of women (n = 17) with a mean weight loss of 37.4, (SD 9.3) kg, whole blood Pb concentrations increased by 90% from mean 1.9 (SD 1.4) µg/dL to 3.9 (SD 3.4) µg/dL after six months [8], an increase comparable to what we observed.

As about 80% of the patients undergoing bariatric surgery are women, many of childbearing age [10], the increase in whole blood Pb concentrations observed one year after surgery is of concern. Weight loss is associated with improved fertility rates [11]. There is no international consensus concerning the ideal time to conception after bariatric surgery, but the standard recommendation is to delay pregnancy for at least 1–1.5 years after surgery [36]. During pregnancy, maternal blood Pb concentrations increase, and Pb is easily transferred across the placenta to the fetus [37]. After birth, Pb is secreted into breast milk [37,38]. As even low levels of Pb exposure in children are associated with neurodevelopmental deficits [39,40], the observed increase in whole blood Pb concentrations after bariatric surgery is worrying.

5.2. Mercury

Compared to French adults [31], median whole blood Hg concentrations were lower in obese Norwegian adults both before and after surgery (Table 4). Obese Norwegian women of reproductive age had lower median Hg concentrations both before and after bariatric surgery compared to age-matched Scandinavian women [32–34] (Table 4).

Before surgery, gender and seafood intake were the strongest determinants for Hg, relations also reported by others [32]. We observed a higher median whole blood Hg concentration in patients with hypertension before surgery. Mercury has numerous negative vascular effects and the clinical consequences of mercury toxicity include, among others, hypertension [5].

There are no published data on Hg levels after bariatric surgery. We observed a reduction in whole blood Hg after bariatric surgery induced weight loss. The reasons for this reduction is unknown, however, gastric bypass surgery reduces the size of the functional stomach and results in restricted food intake. As whole blood Hg has a relatively short half-life of approximately 50 days [30], a reduced intake of fish and seafood after surgery may be responsible for the reduced whole blood Hg concentrations.

5.3. Cadmium

Compared to French adults [31], median whole blood Cd concentrations were lower in obese Norwegian adults both before and after surgery (Table 4). Median Cd concentrations were higher in obese Norwegian women before surgery compared to other Scandinavian women [32–34] (Table 4). After surgery, median Cd levels were reduced in obese women resembling age-matched Danish women [34] (Table 4).

The strongest determinants for Cd concentrations before surgery were use of tobacco, as reported earlier [32,33,41]. There are no published data on whole blood Cd concentrations after bariatric surgery. Whole blood Cd is an established marker of Cd exposure and is reported to also reflect short term fluctuations in exposure [29]. As the percentage of daily smokers was substantially reduced one year after surgery, this may partially explain the observed reduction in whole blood Cd concentrations.

6. Conclusion

In this study of obese Norwegian adults whole blood concentrations of Pb, Hg and Cd were weakly negatively related to BMI. However, the weight loss induced by bariatric surgery increased median whole blood Pb significantly, whereas it reduced Hg and Cd concentrations as measured one year after surgery. Weight loss is known to increase fertility, and as the majority of bariatric surgery patients are women of reproductive age, this increase in whole blood PB concentrations is of concern.

Interestingly, patients with hypertension had significantly higher median whole blood Hg concentrations before surgery, but not postoperatively, while no differences in Pb, Hg or Cd concentrations were seen as related to a diagnosis of diabetes.

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Declarations of interests

The authors declare no conflicts of interest.

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